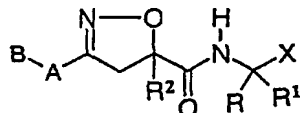


Claims

[1] 1. A compound of the following formula (1):

[2]



(1)

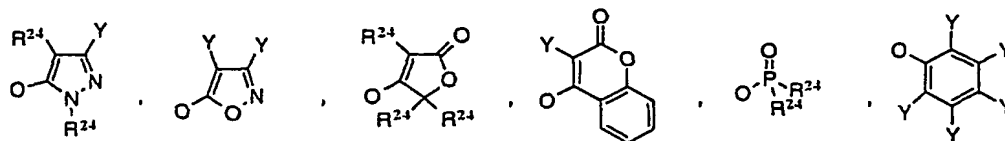
in which

- I) R represents H, simple alkyl chain (-SAC), simple cycloalkyl chain (-SCAC), aryl group (-Ar), or simple alkyl chain substituted by aryl (-SAC-Ar),
- [3] II) R¹ represents -SAC, -SCAC, -Ar, -SAC-Ar, or a side chain residue of all the natural amino acids; and the compound of formula (1) may exist in a specific diastereomeric form, or mixtures thereof when the carbon to which R¹ is attached becomes a stereocenter due to the R¹ group; or the compound of formula (1) may have a protecting group in an ester form (-CO R³ wherein R³ is -SAC) or a sulfonamide form (-CONHSO₂ R⁴ wherein R⁴ is -SAC), or may exist in the form of pharmaceutically acceptable salt, when R¹ is a side chain residue of an amino acid containing carboxyl moiety; or the compound of formula (1) may also exist in the form of pharmaceutically acceptable salt when R¹ is a side chain residue of an amino acid containing a base moiety,
- III) R² represents -SAC, -SCAC, -Ar, -SAC-Ar, or a side chain residue of the natural amino acids; and the compound of formula (1) may exist in a specific diastereomeric form, or mixtures thereof when the carbon to which R² is attached becomes a stereocenter due to the R² group; the compound of formula (1) may have a protecting group in an ester form (-CO R⁵ wherein R⁵ is -SAC) or a sulfonamide form (-CONHSO₂ R⁶ wherein R⁶ is -SAC), or may exist in the form of pharmaceutically acceptable salt, when R² is a side chain residue of an amino acid containing carboxyl moiety; or the compound of formula (1) may also exist in the form of pharmaceutically acceptable salt when R² is a side chain residue of an amino acid containing a base moiety, or
- R² further represents H; -(CH₂)_n OR⁷ wherein R⁷ is -SAC, -SCAC, -Ar, or -SAC-Ar, and n = 1 or 2; or -(CH₂)_n OC(=O)R⁸ wherein R⁸ is -SAC, -SCAC, -Ar, or -SAC-Ar, and n = 1 or 2,
- IV) A represents -(CH₂)_n - (n = 0-4), -O-(CH₂)_n - (n = 0-4), or -NR⁹-(CH₂)_n - (n = 0-4) wherein R⁹ is -SAC, -SCAC, -Ar, or -SAC-Ar,

V) Represents H, -SAC, -SCAC, -Ar, or -SAC-Ar, or

VI) R and R¹ may form a cycle together with the carbon atom to which they are attached, where -R-R¹- is -(CH₂)_n-, -(CH₂)_n-O-(CH₂)_m-, or -(CH₂)_n-NR¹⁰-(CH₂)_m- wherein n+m<9 and R¹⁰ is -SAC, -SCAC, -Ar, -SAC-Ar, -C(=O)-SAC, -C(=O)-SCAC, -C(=O)-Ar, or -C(=O)-SAC-Ar,

VII) X represents -C(=O)CH₂OR¹¹ wherein R¹¹ is -SAC, -SCAC, -Ar, or -SAC-Ar; -C(=O)CH₂OC(=O)R¹² wherein R¹² is -SAC, -SCAC, -Ar, or -SAC-Ar; -CH=CH-CO R¹³ wherein R¹³ is -SAC, -SCAC, -Ar, or -SAC-Ar; -CH=CH-SO₂R¹⁴ wherein R¹⁴ is -SAC, -SCAC, -Ar, or -SAC-Ar; -C(=O)CH=CH₂; or -COCH₂-W wherein W is -N₂, -F, -Cl, -Br, -I, -NR¹⁵R¹⁶ (R¹⁵ and R¹⁶ each are -SAC, -SCAC, -Ar, or -SAC-Ar, or together may form 3- to 6-membered saturated or unsaturated cyclic group), -SR¹⁷ (R¹⁷ is -SAC, -SCAC, -Ar, or -SAC-Ar), or is the following formula:



wherein

Y is H, -OH, -OR¹⁸ (R¹⁸ = -SAC or -SCAC), -C(=O)R¹⁹ (R¹⁹ = -H, -SAC, or -SCAC), -F, -Cl, -Br, -I, -CN, -NC, -N₃, -CO₂H, CF₃, -CO₂R²⁰ (R²⁰ = -SAC or -SCAC), -C(=O)NHR²¹ (R²¹ = -SAC or -SCAC), or -C(=O)NR²²R²³ (R²² and R²³ each are -SAC, -SCAC, -Ar, or -SAC-Ar),

R²⁴ is H, -SAC, -SAC-Ar, or -Ar, salt, or stereoisomer thereof.

- [4] 2. The compound according to claim 1 wherein R represents H.
- [5] 3. The compound according to claim 1 wherein R¹ represents -CH₂COOH, -CH₂COOR³ (R³=SAC), or -CH₂CONHSO₂R⁴ (R⁴ = SAC).
- [6] 4. The compound according to claim 1 wherein R² represents H, -SAC, -Ar, or -(CH₂)_nOR⁷ (R⁷ = -SAC, -SCAC, -Ar, or -SAC-Ar, and n = 1 or 2).
- [7] 5. The compound according to claim 1 wherein X represents -C(=O)CH₂OAr, -C(=O)CH₂OC(=O)Ar, or -COCH₂-W wherein W is -N₂, -F, -Cl, -Br, -I, -NR¹⁵R¹⁶ (R¹⁵ and R¹⁶ each are -SAC, -SCAC, -Ar, or -SAC-Ar, or together may form 3- to 6-membered saturated or unsaturated cyclic group), or -SR¹⁷ (R¹⁷ is -SAC, -SCAC, -Ar, or -SAC-Ar).
- [8] 6. The compound according to claim 1 wherein
 - I) R represents H,

II) R^1 represents $-\text{CH}_2\text{COOH}$, $-\text{CH}_2\text{COOR}^3$ ($R^3 = \text{SAC}$), or $-\text{CH}_2\text{CONHSO}_2\text{R}^4$ ($R^4 = \text{SAC}$),

III) R^2 represents H, -SAC, -Ar, or $-(\text{CH}_2)_n\text{OR}^7$ ($R^7 = -\text{SAC}$, -SCAC, -Ar, or -SAC-Ar, and $n = 1$ or 2),

IV) A represents $-(\text{CH}_2)_n-$ ($n = 0-4$) or $-\text{O}-(\text{CH}_2)_n-$ ($n = 0-4$),

V) B represents H, -SAC, -SCAC, -Ar, or -SAC-Ar,

VI) X represents $-\text{COCH}_2\text{N}_2$, $-\text{COCH}_2\text{F}$, $-\text{COCH}_2\text{Cl}$, $-\text{COCH}_2\text{Br}$, $-\text{COCH}_2\text{I}$, $-\text{COCH}_2\text{OAr}$, $-\text{COCH}_2\text{OCOAr}$ or $-\text{COCH}_2\text{SR}^{17}$ (R^{17} is -SAC, -SCAC, -Ar or -SAC-Ar).

[9] 7. The compound according to claim 1 which is selected from the following group:

- (1) (3*S*)-5-[(2,6-dichlorobenzoyl)oxy] - 3-([5-methyl-3-phenyl-4,5-dihydro-5-isoxazolyl]carbonyl)amino)-4-oxopentanoic acid (Iaa);
- (2) (3*S*)-3-([5-methyl-3-phenyl-4,5-dihydro-5-isoxazolyl]carbonyl)amino)-4-oxo-5-phenoxy-pentanoic acid (Ibb);
- (3) (3*S*)-3-([5-ethyl-3-phenyl-4,5-dihydro-5-isoxazolyl]carbonyl)amino)-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)pentanoic acid (Icc);
- (4) (3*S*)-3-([5-ethyl-3-(1-naphthyl)-4,5-dihydro-5-isoxazolyl]carbonyl)amino)-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)pentanoic acid (Idd);
- (5) (3*S*)-3-([5-ethyl-3-(2-naphthyl)-4,5-dihydro-5-isoxazolyl]carbonyl)amino)-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)pentanoic acid (Iee);
- (6) (3*S*)-3-([5-ethyl-3-(1-isoquinolyl)-4,5-dihydro-5-isoxazolyl]carbonyl)amino)-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)pentanoic acid (Iff);
- (7) 3-([5-ethyl-3-(1-isoquinolyl)-4,5-dihydro-5-isoxazolyl]carbonyl)amino)-5-fluoro-4-oxopentanoic acid (Igg);
- (8) ethyl 3-([5-ethyl-3-(1-isoquinolyl)-4,5-dihydro-5-isoxazolyl]carbonyl)amino)-5-fluoro-4-oxopentanoate (Ihh);
- (9) 5-fluoro-3-([(5*R*)-5-isopropyl-3-(1-isoquinolyl)-4,5-dihydro-5-isoxazolyl]carbonyl)amino)-4-oxopentanoic acid (Iii);
- (10) 3-([5-ethyl-3-(4-quinolyl)-4,5-dihydro-5-isoxazolyl]carbonyl)amino)-5-fluoro-4-oxopentanoic acid (Ijj);
- (11) 3-([3-(benzothiophen-2-yl)-5-ethyl-4,5-dihydro-5-isoxazolyl]carbonyl)amino)-5-fluoro-4-oxopentanoic acid (Ikk);
- (12) (3*S*)-3-([3-(1,3-dimethyl-1*H*-indol-2-yl)-5-ethyl-4,5-dihydro-5-isoxazolyl]

- carbonyl}amino)-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)pentanoic acid (Imm);
- (13) 3-([3-(1,3-dimethyl-1*H*-indol-2-yl)-5-ethyl-4,5-dihydro-5-isoxazolyl] carbonyl}amino)-5-fluoro-4-oxopentanoic acid (Imm);
- (14) (3*S*)-3-([5-ethyl-3-(1-naphthylmethyl)-4,5-dihydro-5-isoxazolyl] carbonyl}amino)-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)pentanoic acid (Inn);
- (15) (3*S*)-5-[(2,6-dichlorobenzoyl)oxy]-3-([5-ethyl-3-[2-(1-naphthyl)ethyl]-4,5-dihydro-5-isoxazolyl] carbonyl}amino)-4-oxopentanoic acid (Ioo);
- (16) (3*S*)-3-([5-ethyl-3-[(1-naphthyloxy)methyl]-4,5-dihydro-5-isoxazolyl] carbonyl}amino)-4-oxo-5-(2,3,5,6-tetrafluorophenoxy) pentanoic acid (Ipp);
- (17) (3*S*)-3-([3-[(4-chloro-1-naphthyl)oxy] methyl]-5-ethyl-4,5-dihydro-5-isoxazolyl] carbonyl}amino)-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)pentanoic acid (Iqq);
- (18) (3*S*,4*E*)-6-ethoxy-3-([(5*R*)-5-isopropyl-3-(1-isoquinolyl)-4,5-dihydro-5-isoxazolyl] carbonyl}amino)-6-oxo-4-hexenoic acid (Irr);
- (19) (3*S*,4*E*)-3-([(5*R*)-5-isopropyl-3-(1-isoquinolyl)-4,5-dihydro-5-isoxazolyl] carbonyl}amino)-5-(methylsulfonyl)-4-pentenoic acid (Iss);
- (20) 5-fluoro-3-([(5*S*)-3-(1-isoquinolyl)-5-propyl-4,5-dihydro-5-isoxazolyl] carbonyl}amino)-4-oxopentanoic acid (Itt);
- (21) 3-([(5*S*)-5-ethyl-3-(1-naphthyl)-4,5-dihydro-5-isoxazolyl] carbonyl}amino)-5-fluoro-4-oxopentanoic acid (Iuu);
- (22) 3-([(5*S*)-5-ethyl-3-(2-quinolyl)-4,5-dihydro-5-isoxazolyl] carbonyl}amino)-5-fluoro-4-oxopentanoic acid (Ivv);
- (23) 3-([(5*R*)-5-ethyl-3-(3-isoquinolyl)-4,5-dihydro-5-isoxazolyl] carbonyl}amino)-5-fluoro-4-oxopentanoic acid (Iww);
- (24) 3-([5-ethyl-3-(8-quinolyl)-4,5-dihydro-5-isoxazolyl] carbonyl}amino)-5-fluoro-4-oxopentanoic acid (Ixx);
- (25) 3-([5-ethyl-3-(3-quinolyl)-4,5-dihydro-5-isoxazolyl] carbonyl}amino)-5-fluoro-4-oxopentanoic acid (Iyy);
- (26) 5-fluoro-3-([(5*R*)-5-isopropyl-3-(2-quinolyl)-4,5-dihydro-5-isoxazolyl] carbonyl}amino)-4-oxopentanoic acid (Izz);
- (27) 3-([5-ethyl-3-(2-isopropylphenyl)-4,5-dihydro-5-isoxazolyl] carbonyl}amino)-5-fluoro-4-oxopentanoic acid (Iaa1);
- (28) 3-([3-[3-(*tert*-butyl)phenyl] -

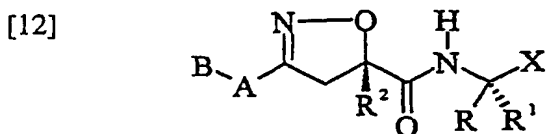
- 5-ethyl-4,5-dihydro-5-isoxazolyl}carbonyl)amino]-5-fluoro-4-oxopentanoic acid (Iaa2);
- (29) 3-[(3-[4-(*tert*-butyl)phenyl] - 5-ethyl-4,5-dihydro-5-isoxazolyl}carbonyl)amino]-5-fluoro-4-oxopentanoic acid (Iaa3);
- (30) 5-fluoro-3-([(5*R*)-5-isopropyl-3-(2-isopropylphenyl)-4,5-dihydro-5-isoxazolyl}carbonyl)amino)-4-oxopentanoic acid (Iaa4);
- (31) 3-([(5*R*)-3-[3-(*tert*-butyl)phenyl]-5-isopropyl-4,5-dihydro-5-isoxazolyl}carbonyl)amino]-5-fluoro-4-oxopentanoic acid (Iaa5);
- (32) 3-([(3-[1,1'-biphenyl]-3-yl-5-isopropyl-4,5-dihydro-5-isoxazolyl}carbonyl)amino)-5-fluoro-4-oxopentanoic acid (Iaa6);
- (33) 3-([(5-ethyl-3-(2-pyridinyl)-4,5-dihydro-5-isoxazolyl}carbonyl)amino)-5-fluoro-4-oxopentanoic acid (Iaa7);
- (34) 3-[(3-[4-(*tert*-butyl)-2-pyridinyl] - 5-ethyl-4,5-dihydro-5-isoxazolyl}carbonyl)amino]-5-fluoro-4-oxopentanoic acid (Iaa8);
- (35) 3-([(5*R*)-3-[4-(*tert*-butyl)-2-pyridinyl] - 5-isopropyl-4,5-dihydro-5-isoxazolyl}carbonyl)amino]-5-fluoro-4-oxopentanoic acid (Iaa9);
- (36) 3-([(5-ethyl-3-(4-isobutyl-2-pyridinyl)-4,5-dihydro-5-isoxazolyl}carbonyl)amino)-5-fluoro-4-oxopentanoic acid (Iaa10);
- (37) 3-([(3-(4-acetyl-2-pyridinyl)-5-ethyl-4,5-dihydro-5-isoxazolyl}carbonyl)amino)-5-fluoro-4-oxopentanoic acid (Iaa11);
- (38) 3-([(3-(4-cyclopropyl-2-pyridinyl)-5-ethyl-4,5-dihydro-5-isoxazolyl}carbonyl)amino)-5-fluoro-4-oxopentanoic acid (Iaa12);
- (39) 3-([(3-(4-cyclopentyl-2-pyridinyl)-5-ethyl-4,5-dihydro-5-isoxazolyl}carbonyl)amino)-5-fluoro-4-oxopentanoic acid (Iaa13);
- (40) 3-([(5*R*)-3-(4-cyclopentyl-2-pyridinyl)-5-isopropyl-4,5-dihydro-5-isoxazolyl}carbonyl)amino)-5-fluoro-4-oxopentanoic acid (Iaa14);
- (41) 3-([(3-(4-cyclohexyl-2-pyridinyl)-5-ethyl-4,5-dihydro-5-isoxazolyl}carbonyl)amino)-5-fluoro-4-oxopentanoic acid (Iaa15);
- (42) 3-([(5-ethyl-3-(5,6,7,8-tetrahydro-1-isoquinolyl)-4,5-dihydro-5-isoxazolyl}carbonyl)amino)-5-fluoro-4-oxopentanoic acid (Iaa16);

- (43) 5-fluoro-3-([5-isopropyl-3-(4-phenyl-2-pyridinyl)-4,5-dihydro-5-isoxazolyl]carbonyl)amino)-4-oxopentanoic acid (Iaa17);
- (44) (3*S*)-5-[(diphenylphosphoryl)oxy]-3-([5*R*)-5-isopropyl-3-(1-isoquinolinyl)-4,5-dihydro-5-isoxazolyl]carbonyl)amino)-4-oxopentanoic acid (Iaa18);
- (45) (3*S*)-3-([5*R*)-5-isopropyl-3-(1-isoquinolinyl)-4,5-dihydro-5-isoxazolyl]carbonyl)amino)-4-oxo-5-{[1-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-5-yl]oxy}pentanoic acid (Iaa19);
- (46) (3*S*)-5-[(4-benzyl-5-oxo-2,5-dihydro-3-furanyl)oxy]-3-([5*R*)-5-isopropyl-3-(1-isoquinolinyl)-4,5-dihydro-5-isoxazolyl]carbonyl)amino)-4-oxopentanoic acid (Iaa20);
- (47) (3*S*)-5-(isobutyryloxy)-3-([5*R*)-5-isopropyl-3-(1-isoquinolinyl)-4,5-dihydro-5-isoxazolyl]carbonyl)amino)-4-oxopentanoic acid (Iaa21);
- (48) (3*S*)-3-([5*R*)-5-isopropyl-3-(1-isoquinolinyl)-4,5-dihydro-5-isoxazolyl]carbonyl)amino)-4-oxo-5-hexenoic acid (Iaa22);
- (49) (3*S*)-3-([5*R*)-5-isopropyl-3-(1-isoquinolinyl)-4,5-dihydro-5-isoxazolyl]carbonyl)amino)-4-oxo-5-(2-pyridinyloxy)pentanoic acid (Iaa23);
- (50) (3*S*)-3-([5-ethyl-3-(2-isopropylphenyl)-4,5-dihydro-5-isoxazolyl]carbonyl)amino)-4-oxo-5-(2-pyridinyloxy)pentanoic acid (Iaa24);
- (51) 2-[(3*S*)-4-carboxy-3-([5*R*)-5-isopropyl-3-(1-isoquinolinyl)-4,5-dihydro-5-isoxazolyl]carbonyl)amino)-2-oxobutyl]oxy)-1-methylpyridinium trifluoromethanesulfonate (Iaa25);
- (52) 2-[(3*S*)-4-carboxy-3-([5-ethyl-3-(2-isopropylphenyl)-4,5-dihydro-5-isoxazolyl]carbonyl)amino)-2-oxobutyl]oxy)-1-methylpyridinium trifluoromethanesulfonate (Iaa26);
- (53) 3-([3-(5-chloro-1-methyl-1*H*-indol-2-yl)-5-isopropyl-4,5-dihydro-5-isoxazolyl]carbonyl)amino)-5-fluoro-4-oxopentanoic acid (Iaa27);
- (54) 3-([3-(1,5-dimethyl-1*H*-indol-2-yl)-5-isopropyl-4,5-dihydro-5-isoxazolyl]carbonyl)amino)-5-fluoro-4-oxopentanoic acid (Iaa28); and
- (55) (3*S*)-5-fluoro-3-([5*R*)-5-isopropyl-3-(1-isoquinolinyl)-4,5-dihydro-5-isoxazolyl]carbonyl)amino)-4-oxopentanoic acid (Iaa29);

xopentanoic acid (Iii-1).

[10] 8. The compound according to claim 1 which is 5-fluoro-3-(((5*R*)-5-isopropyl-3-(1-isoquinoliny)-4,5-dihydro-5-isoxazolyl]carbonyl}amino)-4-oxopentanoic acid (Iii).

[11] 9. A compound of the following formula (1a):



[13] (1a)

in which

A, B, R, R¹, R², and X are defined as described in claim 1.

[14] 10. The compound according to claim 9 which is (3*S*)-5-fluoro-3-(((5*R*)-5-isopropyl-3-(1-isoquinoliny)-4,5-dihydro-5-isoxazolyl]carbonyl}amino)-4-oxopentanoic acid (Iii-1).

[15] 11. A process for preparing the compound (Iii-1) as defined in claim 10, which comprises the steps of dissolving a mixture of (3*S*)-5-fluoro-3-(((5*R*)-5-isopropyl-3-(1-isoquinoliny)-4,5-dihydro-5-isoxazolyl]carbonyl}amino)-4-oxopentanoic acid and (3*R*)-5-fluoro-3-(((5*R*)-5-isopropyl-3-(1-isoquinoliny)-4,5-dihydro-5-isoxazolyl]carbonyl}amino)-4-oxopentanoic acid in methyl t-butyl ether, adding a small amount of crystalline (3*S*)-5-fluoro-3-(((5*R*)-5-isopropyl-3-(1-isoquinoliny)-4,5-dihydro-5-isoxazolyl]carbonyl}amino)-4-oxopentanoic acid as a seed material to give a crystal, and recrystallizing this crystal from ethyl acetate/n-hexane solvent system.

[16] 12. A therapeutic composition for preventing inflammation and apoptosis comprising the caspase inhibitor compound of formula (1), salt, or stereoisomer thereof as defined in claim 1 as an active ingredient together with the pharmaceutically acceptable carrier.

[17] 13. The composition according to claim 12 for the treatment of dementia, cerebral stroke, brain impairment due to AIDS, diabetes, gastric ulcer, cerebral injury by hepatitis, hepatitis-induced hepatic diseases, acute hepatitis, fulminant hepatic failure, liver cirrhosis, sepsis, organ transplantation rejection, rheumatic arthritis, or cardiac cell apoptosis due to ischemic cardiac diseases.

[18] 14. The composition according to claim 12 for the treatment of acute hepatitis or liver cirrhosis.

- [19] 15. The composition according to claim 12 for the treatment of rheumatic arthritis.
- [20] 16. The composition according to claim 12 which is formulated as an oral preparation, an injection, or a patch.
- [21] 17. The composition according to claim 12 comprising the compound (Iii) as defined in claim 8 as an active ingredient.
- [22] 18. The composition according to claim 12 comprising the compound (Iii-1) as defined in claim 10 as an active ingredient.
- [23] 19. A process for preparing the therapeutic composition for preventing inflammation and apoptosis as defined in claim 12, comprising admixing the caspase inhibitor compound of formula (1), salt, or stereoisomer thereof as defined in claim 1 with pharmaceutically acceptable carrier.
- [24] 20. A method for preventing inflammation and apoptosis, comprising administering an effective amount of the caspase inhibitor compound of formula (1), salt, or stereoisomer thereof as defined in claim 1 to a patient suffering from inflammation and apoptosis.
- [25] 21. A use of the caspase inhibitor compound of formula (1), salt, or stereoisomer thereof as defined in claim 1 for preventing inflammation and apoptosis.